Remarks

1. Claim Objections

Claims 12-15 and 17-18 are objected to under 37 C.F.R. 1.75(c) as being of improper dependent form. Claim 12 has been cancelled without prejudice or disclaimer, making the objection as to this claim moot. Applicants have amended independent claim 9, from which claims 13-15 and 17-18 depend, and, in view of this amendment, respectfully request that the objection be withdrawn.

2. Claim Rejections-35 U.S.C. § 112

Claims 1-5 are rejected under 35 U.S.C. § 112, second paragraph. Applicants have amended claims 1-4 to remove the term "highly pure." In view of this amendment, applicants respectfully request that the rejection be withdrawn.

3. Claim Rejections-35 U.S.C. § 102

Claims 1-3, 7, and 9 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Sas et al. (EP 389035 A1) ("Sas"). Applicants respectfully traverse the rejection.

Applicants respectfully submit that the presently claimed invention is not anticipated by Sas. As amended, independent claim 1 recites a composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one comprising (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount less than 0.5% by weight. Claims 2 and 3 depend from claim 1.

In contrast, Sas discloses a pharmaceutical composition having a crystalline pure form of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one is known to be polymorphous and has two crystalline pure forms, referred to as "Form 1" and "Form 2." The two crystalline forms are structurally identical but differ in their conformations. Specifically, the A ring of Form 1 is 2β,3α half chair while the A ring of Form 2 is 2α,3β half chair. Sas discloses methods of preparing both Form 1 and Form 2 using different crystallization conditions. These methods provide crystalline pure forms of Form 1 and Form 2, which means that the

composition of one crystalline form of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, *i.e.,* Form 1, is substantially free of the other crystalline form, *i.e.,* Form 2.

Sas does not disclose that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is present in an amount less than 0.5% by weight in a composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. Rather, the purities disclosed in Example 1-8 of Sas are the crystalline purities of Form 1 and Form 2 of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. These purities are determined by DRIFT analyses. Therefore, the 97.2% purity disclosed in Example 2 only shows that Sas obtained a 97.2% crystalline purity of Form 1 of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. Nothing in Sas discloses that compounds different from (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one are present in the composition, let alone that any such impurities are (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one. Furthermore, as known in the art, DRIFT analyses are not suitable for detecting impurities at a level below 1% and, therefore, Sas could not disclose the presence of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount less than 0.5% by weight.

Since Sas does not disclose that an impurity in its composition is (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one or that this impurity is present in an amount less than 0.5% by weight, Sas cannot anticipate claim 1.

The Examiner's argument that Sas anticipates claim 1 because Sas is silent about impurities (and, therefore, discloses 0% by weight of the impurity) fails because Sas does not disclose (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one as an impurity. As previously discussed, Sas does not disclose this impurity in its composition because Sas discloses a crystalline pure form of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. Furthermore, the DRIFT analyses used in Sas are not suitable for detecting impurities below 1% and would not detect the amount of impurity recited in claim 1.

Since Sas does not disclose every element of claim 1, applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn. Applicants also request that the rejection of claims 2-3, which depend directly from claim 1, be withdrawn.

As amended, independent claim 7 recites a pharmaceutical dosage unit comprising a pharmaceutically suitable solid carrier and a composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, which comprises (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount less than 0.5% by weight.

Since Sas does not disclose that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is present in its composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, applicants respectfully request that the rejection of claim 7 be withdrawn for the same reasons presented above.

As amended, independent claim 9 recites a dosage unit comprising a pharmaceutically suitable solid carrier and (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in an amount of less than 2.50 mg and comprising less than 5% by weight of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one at a shelf-life of at least 1.5 years. Since Sas does not disclose that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is present in its composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, applicants respectfully request that the rejection of claim 9 be withdrawn for the same reasons presented previously. Claim 9 is further allowable because Sas does not disclose that the dosage unit comprises less than 5% by weight of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one at a shelf-life of at least 1.5 years.

4. Claim Rejections-35 U.S.C. § 103

A. Claims 4-6 - Sas and van Vliet

Claims 4-6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sas and van Vliet et al. (*Recueil des Travaux Chimiques des Pays-Bas*, April 1986, 105/4:111-115) ("van Vliet"). Applicants respectfully traverse this rejection, as hereinafter set forth.

Applicants respectfully submit that claims 4-6 are not rendered obvious by Sas. As discussed previously herein, Sas discloses a crystalline pure pharmaceutical composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, where the two forms of the polymorphous compound are crystallized using different conditions.

As amended, claim 4 recites a process for preparing (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one comprising aging crystals of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in the presence of water for at least 24 hours, wherein the (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one comprises (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount less than 0.5% by weight. Claims 5 and 6 depend directly on claim 4.

Since Sas does not teach or suggest that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is present as an impurity, as previously discussed, Sas does not teach or suggest that this impurity is present in an amount less than 0.5% by weight. Sas also does not teach or suggest that its composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one is prepared by aging the crystals.

van Vliet fails to correct these deficiencies in Sas. van Vliet discloses an alternative method of synthesizing (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one. While van Vliet teaches that (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one (labeled as Compound 21) is a potential impurity in this synthesis, van Vliet only discloses that the impurity is present at less than 1%. *See,* van Vliet, p.113. van Vliet does not does teach or suggest that the impurity is present in an amount less than 0.5% by weight. Furthermore, van Vliet does not teach or suggest aging the crystals to prepare (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one, as recited in claim 4.

Nothing in Sas or van Vliet teaches or suggests aging the crystals of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one to improve the purity and the stability of the compound. In addition, there is no motivation in either of these references to age the crystals. Rather, it is known to a person of ordinary skill in the art that the quality of crystals typically does not improve if the crystals are allowed to age in the presence of residual solvents for a long period of time. Therefore, aging the crystals to produce a more pure and more stable (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one is a surprising and unexpected result and, accordingly, is not obvious.

The Examiner argues as further evidence of obviousness that there is no side by side comparison of the claimed invention and the cited art. However, the process recited in claim 4 is clearly shown to result

in (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one having a higher purity and a higher stability than the cited art. In Example 1 of the as-filed application, the method of preparing (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one is similar to the method disclosed in Sas. Example 1 also uses the recrystallization step described in Example 4 of Sas. In contrast, in Example 2 of the as-filed application, the (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one is prepared by aging crystals of the compound. A comparison of the results in Examples 1 and 2 shows that the composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one prepared by aging the crystals had a higher purity and stability than the composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one prepared without aging the crystals.

As the proposed combination of Sas and van Vliet fails to teach or suggest every element of the presently claimed invention, applicants respectfully submit that the presently claimed invention is not obvious over the combination of references. Reconsideration is respectfully requested.

B. Claims 10-18 - Sas and van Vliet

Claims 10-18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sas and van Vliet. Claim 12 has been cancelled without prejudice or disclaimer, making the rejection of claim 12 moot. Applicants respectfully traverse this rejection as to the remaining claims, as hereinafter set forth.

Claims 10, 11, and 13-18 depend from claim 9 and, therefore, include the limitation that the dosage unit comprises less than 5% by weight of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one at a shelf-life of at least 1.5 years. Neither Sas nor van Vliet teaches or suggests that the impurity is present at less than 5% by weight at a shelf-life of at least 1.5 years. Therefore, applicants respectfully submit that the presently claimed invention is not obvious over this combination of references. Reconsideration is respectfully requested.

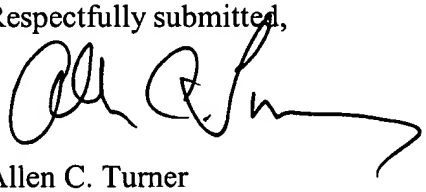
The Examiner also states that claims 10, 11, and 13-18 are obvious because the optimization of active ingredients is within the skill of a person of ordinary skill in the art. However, since the cited art does not teach or suggest all the limitations of independent claim 9, the rejection of dependent claims 10, 11, and 13-18 is improper.

The Examiner cites as further evidence of obviousness that no side by side comparison exists of the claimed invention and the cited art. However, as previously mentioned, a side by side comparison is shown in Examples 1 and 2 of the as-filed application. The composition of Example 2 is formulated into a dosage unit, as described in Examples 4-6. Therefore, the specification supports the nonobviousness of the claimed invention over the cited art.

CONCLUSION

In view of the remarks, applicants respectfully submit that the claims define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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N:\1963\5047\Response to 2nd OA rev.wpd

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice amended) [Highly pure] A composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one comprising (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount less than 0.5% by weight.

2. (Twice amended) [The highly pure (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one] The composition according to claim 1, wherein the amount of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is 0.25% or less.

3. (Twice amended) [The highly pure (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one] The composition according to claim 1, wherein the amount of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one is 0.1% or less.

4. (Twice amended) A process for preparing [the highly pure] (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one [of claim 1,] comprising aging crystals of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in the presence of water for at least 24 hours.

7. (Twice amended) A pharmaceutical dosage unit comprising a pharmaceutically suitable solid carrier and [the highly pure] a composition of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one [of claim 1] comprising (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one in an amount less than 0.5% by weight.

9. (Twice amended) A dosage unit comprising a pharmaceutically suitable solid carrier and (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-5(10)-en-20-yn-3-one in an amount of less than 2.50 mg[, which is] and comprising less than 5% by weight of (7α, 17α)-17-hydroxy-7-methyl-19-nor-17-pregn-4-en-20-yn-3-one at a shelf-life of at least 1.5 years.